REMARKS

Claims 1, 2, 13, 14, 27 and 50-64 are pending in the subject application. Applicant has hereinabove cancelled claims 13, 14, 51, 52, 54-61, 63 and 64 without disclaimer or prejudice to the right to pursue the subject matter of these claims in a future application. Applicant has also hereinabove amended claims 1, 2, 27, 50, 53, and 62 and added new claims 65-67. Support for these amendments may be found *inter alia* in the subject specification as follows: claims 1 and 2: page 26, line 29 - page 27, line 4; page 34, line 25; claim 27: page 26, line 29 - page 27, line 4; page 34, line 25; page 38, lines 18-19 and 26; claims 50, 53 and 62: page 26, line 29 - page 27, line 4; and claims 65-67: page 34, line 15. Applicant maintains that none of the amendments to the claims or the specification raise any issue of new matter. Accordingly, entry of this amendment is respectfully requested such that claims 1, 2, 27, 50, 53, 62, and 65-67 will be pending.

In view of the arguments and amendments set forth below, applicant maintains that the grounds of the Examiner's rejection set forth in the February 13, 2007 Office Action have been overcome and respectfully requests that the Examiner reconsider and withdraw these grounds of rejection.

Objection to the Specification

The Examiner objected to the disclosure for the following reasons: (i) an updated status of the parent nonprovisional application should be included in the first sentence of the specification. For example, a statement reading "This invention is a continuation-in-part and claims priority to U.S. Serial No. 09/553,927, filed April 21, 2000, now abandoned..." should be

entered; and (ii) the reference cited on page 48, lines 15-16 (Yao et al.) should be updated.

In response, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended the specification to address the Examiner's objections. Applicant maintains that none of the amendments to the specification raise any issue of new matter. Accordingly, applicant respectfully request that the Examiner reconsider and withdraw these grounds of objection.

Claim Objections

The Examiner stated that should claim 1 be found allowable, claim 13 will be objected to under 37 CFR §1.75 as being a substantial duplicate thereof.

The Examiner stated that should claim 2 be found allowable, claim 14 will be objected to under 37 CFR §1.75 as being a substantial duplicate thereof.

The Examiner objected to claims 50-61 for allegedly being dependent upon a rejected base claim, but stated that claims 50-61 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In response, without conceding the correctness of the Examiner's position, applicant has hereinabove cancelled claims 13, 14, 51, 52 and 54-61 without disclaimer or prejudice. Therefore, the objection thereto is now moot.

In response to the Examiner's objection to the remaining claims, applicant respectfully traverses. Applicant notes that claims 50 and 53 depend from claims 1 and 2 which are not objected to by the Examiner. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw these grounds of objection.

Claim Rejections Under 35 U.S.C. §112, first paragraph

Enablement

The Examiner rejected claims 1, 2, 13, 14, and 27 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for methods of administering all possible amphiphilic compounds, including a method for inhibiting necrosis, plaque rupture and/or superficial erosion. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

However, the Examiner stated that the specification is enabling for (1) a method for inhibiting macrophage death in a subject having, or at increased risk for developing cardiovascular disease comprising administering the amphiphilic compound, 2β-(2-diethylaminoethoxy)-androstenone (U18666A); (2) a method for inhibiting atherosclerotic lesional complications in a subject having, or at increased risk for developing cardiovascular disease comprising administering the amphiphilic compound, 2β-(2-diethylaminoethoxy)-androstenone (U18666A); and (3) a method for inhibiting atherosclerotic lesional necrosis in a subject having, or at increased risk for developing cardiovascular disease comprising administering the amphiphilic compound, 2β-(2-diethylaminoethoxy)-androstenone (U18666A).

The Examiner stated that the specification allegedly does not teach any methods or working examples to indicate that all possible amphiphilic compounds inhibit macrophage death, inhibit atherosclerotic lesional complications, or inhibit necrosis, plaque rupture, and superficial erosion in a subject having, or at increased risk for developing, cardiovascular disease.

The Examiner asserted that undue experimentation would be required of the skilled artisan to administer all possible amphiphilic compounds to a subject and determine their effect *in vivo*. The Examiner stated that the specification of the instant application teaches that "'amphiphilic compounds' include, without limitation, compounds which inhibit cholesterol esterification (e.g., steroids such as progesterone), hydrophobic amines, phenothiazines, ionophores, cytochalasins, lysophosphatides such as lysophosphatidylcholine, lysophosphatidylserine and lysophosphatidylethanolamine, colchicine, nigericin, chloroquine, chlorpromazine, trifluoperazine, monensin and amphipathic amines such as imipramine and UI8666A". The Examiner stated that however, the state of the art is such that the compounds listed by the specification are structurally and functionally diverse from one another. The Examiner stated that one skilled in the art would not be able to predict that all amphiphilic compounds (except U18666A, as disclosed in the example of the instant specification) would be able to inhibit macrophage death, inhibit atherosclerotic lesional complications, or inhibit necrosis, plaque rupture, and/or superficial erosion in a subject.

In response, without conceding the correctness of the Examiner's position, applicant has hereinabove cancelled claims 13 and 14

without disclaimer or prejudice. Therefore, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's rejection and the expedite prosecution of the subject application has hereinabove amended claims 1, 2 and 27. Claims 1, 2 and 27, as amended, no longer recite "amphiphilic compound" but instead now recite "amphipathic amine."

As the Examiner conceded above, applicant has demonstrated that the amphipathic amine U18666A functions *in vivo* to inhibit macrophage death, atherosclerotic lesional complications and atherosclerotic lesional necrosis.

In the Second Series of Experiments beginning on page 57 of the subject specification applicant describes that the amphipathic amine imipramine behaves similarly to U18666A by inhibiting the intracellular transport of cholesterol in macrophage cells thereby inhibiting macrophage death.

Applicant notes that the compounds U18666A and imipramine share the same properties, i.e. they are both amphipathic amines. In addition, both compounds are active in inhibiting macrophage death. However, the overall structure of these compounds is not similar. Therefore, one of skill in the art would conclude that the activity of these compounds is attributable to their similar properties, i.e. that they are amphipathic amines. It is well known by those of skill in the art that compounds with similar properties function similarly. Accordingly, one of skill in the art would expect that other amphipathic amines would function

similarly to U18666A and imipramine, thereby inhibiting macrophage death *in vivo*, which in turn would inhibit atherosclerotic lesional complications and atherosclerotic lesional necrosis.

Regarding the Examiner's assertion that there are no methods or working examples in the instant specification to indicate that any amphiphilic compound, including U18666A, is able to inhibit all forms/types of necrosis in all possible cells in a subject with cardiovascular disease (other than atherosclerotic lesional necrosis), applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended claim 27 such that it now recites the term "atherosclerotic lesional necrosis."

Regarding the Examiner's assertion that there are no methods or working examples in the instant specification to indicate that any amphiphilic compound, including U18666A, is able to inhibit superficial erosion in a subject, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended claim 27 such that it no longer recites the term "superficial erosion."

With respect to the Examiner's assertion that there are no methods or working examples in the instant specification to indicate that any amphiphilic compound, including U18666A, is able to inhibit plaque rupture, applicant respectfully traverses. Applicant notes that the Examiner hereinabove conceded that in the subject specification applicant demonstrated that

administering the amphipathic amine U18666A *in vivo* inhibited atherosclerotic lesional necrosis. On page 1, lines 29 *et seq.* (see also page 48, last paragraph), applicant describes that atherosclerotic lesional necrotic areas are often found in areas of plaque rupture. Therefore, one of skill in the art would reasonably expect that administering an amphipathic amine such as U18666A or imipramine would also inhibit plaque rupture.

For these reasons, applicant maintains that based on the guidance in the subject specification in combination with what was known by those of skill in the art at the time the subject application was filed, one of skill in the art would be able to make and use the claimed invention without undue experimentation.

In light of the above remarks, applicant maintains that claims 1, 2 and 27 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Written Description

The Examiner rejected claims 1, 2, 13, 14, and 27 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner asserted that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the specification of the instant application teaches that the term "amphiphilic compounds" includes, without limitation, "compounds which inhibit cholesterol esterification (e.g., steroids such as progesterone),

hydrophobic amines, phenothiazines, ionophores, cytochalasins, lysophosphatides such as lysophosphatidylcholine, lysophosphatidylserine and lysophosphatidylethanolamine, colchicine, nigericin, chloroquine, chlorpromazine, trifluoperazine, monensin and amphipathic amines such as imipramine and UI8666A."

The Examiner also asserted that the specification only teaches methods for examining inhibition of intracellular transport of cholesterol in macrophages.

The Examiner further asserted that the state of the art is such that cholesterol is present in all eukaryotic cell membranes.

The Examiner stated that thus, the brief description in the specification of a few examples of amphiphilic compounds and one example of a type of cell is not adequate written description of an entire genus of methods of using a genus of amphiphilic compounds that inhibit intracellular transport of cholesterol in a genus of cells.

The Examiner stated that the skilled artisan cannot envision the amphiphilic compounds and cell types of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

The Examiner stated that therefore, only methods of utilizing a specific amphiphilic compound and targeted cell type, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

In response to the above rejection, but without conceding the correctness thereof, applicant points out that claims 13 and 14 have been canceled. Thus, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended claims 1, 2, and 27 such that these claims no longer recite the term "amphiphilic compound". In addition, applicant has amended claims 1, 2, and 27 such that these claims now recite "amphipathic amine." Furthermore, applicant has hereinabove further amended claims 1, 2, and 27 such that they recite "macrophage cells."

Applicant contends that the subject specification provides adequate written description for the inventions set forth in claims 1, 2 and 27, as amended, evidencing applicant's possession of the claimed invention at the time of filing.

Applicant notes that the term amphipathic amine is described on page 27, lines 4-5. The compounds U18666A and imipramine, which applicant used in the experiments set forth in the subject specification, are examples of amphipathic amines (see page 27, lines 4-5). In the experiments set forth in the Second Series of Experiments beginning on page 57 of the subject specification applicant demonstrates that amphipathic amines such as imipramine and U-18666A inhibit intracellular cholesterol transport thereby preventing macrophage death (claim 1), which in turn inhibits atherosclerotic lesional complications (claim 2), atherosclerotic lesional necrosis and plaque rupture (claim 27). Therefore, applicant maintains that the subject specification adequately

describes the claimed invention.

In light of the above remarks, applicant maintains that claims 1, 2 and 27, as amended, satisfy the written description requirement of 35 U.S.C. §112, first paragraph, and respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 27 and 62-64 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserted that claims 27 and 62-64 are indefinite because the elements recited in the claim do not constitute proper Markush groups. The Examiner stated that the claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations.

The Examiner also rejected claims 27 and 62-64 as being indefinite due to recitation of the phrase "inhibiting necrosis...in a subject having, or at increased risk for developing, cardiovascular disease...." The Examiner stated that the target cell/tissue for the inhibition of necrosis and/or the type of necrosis cannot be determined.

In response, applicant respectfully traverses. Nevertheless, applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended claim 27 such that it no longer recites the term "and/or". In addition, applicant has amended claim 27

such that it now recites "atherosclerotic lesional necrosis."

In view of the above remarks, applicant contends that claim 27, and claims 62-64 which depend therefrom, satisfy the requirements of 35 U.S.C. §112, second paragraph. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw these grounds of rejection.

Claim Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 2, 13, 14, and 27 under 35 U.S.C. §102(b) as allegedly being anticipated by Houser et al. (*Cardiovacular Pathol.* 9(6): 317-322 (2000)).

The Examiner stated that Houser et al. teach that hypercholesterolemic male New Zealand white rabbits are administered doses of progesterone and that high doses of 17-hydroxyprogesterone are significantly associated with less aortic plaque load than controls. The Examiner also noted that it is well known in the prior art that progesterone is an amphiphilic compound and that it inhibits intracellular transport of cholesterol (citing for example, Lange et al. 1994; Mazzone et al. 1995; Aikawa et al. 1994).

In response, without conceding the correctness of the Examiner's position, applicant has hereinabove cancelled claims 13 and 14 without disclaimer or prejudice. Therefore, the rejection thereof is now moot.

In response to the Examiner's rejection of the remaining claims, applicant respectfully traverses. Nevertheless,

applicant without conceding the correctness of the Examiner's position and to expedite prosecution of the subject application has hereinabove amended claims 1, 2 and 27 such that these claims no longer recite the term "amphiphilic compound" but instead now recite "an amphipathic amine." Applicant notes that progesterone is not an amphipathic amine. Houser et al. do not teach any amphipathic amine, and thus fails to teach each and every element of claims 1, 2 and 27, as amended.

In view of the above remarks, applicant contends that claims 1, 2, and 27 satisfy the requirements of 35 U.S.C. §102(b). Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicant respectfully requests that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of pending claims 1, 2, 27, 50, 53, 62 and 65-67.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

8/13/07

John P. White
Reg. No. 28,678

Date